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Measuring the interaction of meal and gastric secretion: a combined quantitative magnetic resonance imaging and pharmacokinetic modeling approach

Sauter, M ; Curcic, J ; Menne, D ; Goetze, O ; Fried, M ; Schwizer, W ; Steingoetter, A

Abstract: BACKGROUND: The stimulation and intragastric accumulation of gastric secretion has been recognized as an important factor in gastroesophageal reflux disease. However, the interaction of gastric secretion and meal emptying has not been fully understood. Current methods to assess gastric secretion are either invasive or unable to provide information on its volume, distribution and dynamics. The aim of this study was to quantify the interaction between meal emptying and meal induced gastric secretion by using quantitative magnetic resonance imaging (MRI) and pharmacokinetic analysis. **METHODS:** A chocolate test meal was developed which is secretion stimulating and MRI compatible. Meal emptying and gastric secretion were assessed in fourteen healthy volunteers using a validated quantitative MRI technique. A population based pharmacokinetic model was developed and applied to the extracted volume data, assessing the meal emptying rate, rate of secretion and their interaction. **KEY RESULTS:** The test meal continuously induced gastric secretion in all subjects, which partly accumulated at the meal-air interface, forming a 'secretion layer' in the proximal stomach. Traditional fitting detected a significant correlation between meal emptying rate and rate of secretion. The pharmacokinetic model quantified this interaction and estimated a 2.3 ± 1 fold higher effect of meal on secretion than vice versa. The efficacy of the emptied meal to produce gastric secretion was 61%. **CONCLUSIONS** 38; **INFERENCES:** The combined quantitative MRI and pharmacokinetic model approach allows for the quantification of gastric secretion volume and its interaction on meal emptying. The observed secretion layer might explain previous findings postulating the presence of an intragastric 'acid pocket'.

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Title: Measuring the interaction of meal and gastric secretion: a combined quantitative MRI and pharmacokinetic modeling approach.

Running title: Interaction of meal and secretion

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Abstract

Background

The stimulation and intragastric accumulation of gastric secretion has been recognized as an important factor in gastroesophageal reflux disease. However, the interaction of gastric secretion and meal emptying has not been fully understood. Current methods to assess gastric secretion are either invasive or unable to provide information on its volume, distribution and dynamics. The aim of this study was to quantify the interaction between meal emptying and meal induced gastric secretion by using quantitative MRI and pharmacokinetic analysis.

Methods:

A chocolate test meal was developed which is secretion stimulating and MRI compatible. Meal emptying and gastric secretion were assessed in fourteen healthy volunteers using a validated quantitative MRI technique. A population based pharmacokinetic model was developed and applied to the extracted volume data, assessing the meal emptying rate, rate of secretion and their interaction.

Key results:

The test meal continuously induced gastric secretion in all subjects, which partly accumulated at the meal-air interface, forming a 'secretion layer' in the proximal stomach. Traditional fitting detected a significant correlation between meal emptying rate and rate of secretion. The pharmacokinetic model quantified this interaction and estimated a 2.3 ± 1 fold higher effect of meal on secretion than vice versa. The efficacy of the emptied meal to produce gastric secretion was 61%.

Conclusions:

The combined quantitative MRI and pharmacokinetic model approach allows for the quantification of gastric secretion volume and its interaction on meal emptying. The observed secretion layer might explain previous findings postulating the presence of an intragastric 'acid pocket'.

Keywords: Quantitative MRI, gastric secretion, gastric emptying, pharmacokinetic modeling

INTRODUCTION

The presence of gastric secretion in the stomach, especially the formation of unbuffered gastric juice near the gastroesophageal junction (GEJ) are considered to represent important parameters for the understanding of gastroesophageal reflux disease (GERD) (1-4). Moreover, gastric secretion might have an effect on the gastric emptying process (5). Current methods to assess gastric secretion are unsatisfactory and often unable to provide new and detailed insights into the pathophysiology of GERD (6). Catheter or capsule based intragastric pH monitoring rely solely on spatially selective pH measurements and therefore provide only limited or no data on the dynamics, distribution and volume of gastric secretion. Aspiration and in vivo intragastric titration (7-9), the two most common methods used to quantify gastric acid secretion are both invasive and may themselves influence the rate and dynamics of secretion (6). Also, catheter migration is an additional problem potentially leading to inaccuracies (6). γ -scintigraphy has been used to image gastric secretion in health and disease (1). This technique, however, relies on the intravenous application of radioactive markers, is restricted to two-dimensional imaging and does not provide anatomical background information

Magnetic Resonance Imaging (MRI) has been proven a valid imaging tool to analyze the physiology of the human gastrointestinal tract. It provides multi-planar and three-dimensional imaging capability, high imaging speed, good spatial resolution and excellent tissue contrast (10-11) (Schwizer, 2006 SJG, Marciani NGM 2011). MRI has recently been proposed for the noninvasive assessment of gastric secretion using a fast T1 mapping sequence (12). By measuring the changes in T1 relaxation times of a MRI contrast agent (DOTAREM[®], Guerbet, Villepinte, France) labeled liquid test meal, this imaging method allowed the separation of drug induced secretion from the test meal (13-14). To date meal induced gastric secretion and its interaction with meal emptying has not yet been analyzed by noninvasive methods.

The aim of this study was to quantify the interaction between meal emptying and meal induced gastric secretion by using quantitative MRI and pharmacokinetic analysis. To this end, the proposed optimized MRI method was applied and a physiological high caloric chocolate test meal was developed which is both highly secretion stimulating and MRI compatible. Meal and secretion volume data were analyzed using a population based pharmacokinetic modeling approach.

MATERIALS AND METHODS

This work presents a MRI sub-investigation in healthy volunteers in the framework of an ongoing clinical study registered at ClinicalTrial.gov with identifier NCT01212614. Written informed consent was obtained from each volunteer; the protocol was approved by the local ethics committee. Fourteen healthy volunteers were studied (8 male, age 26 ± 7.5 years, BMI 23.3 ± 1.9 kg/m²) after a minimum 6-8 hours fast. All volunteers had no evidence of gastrointestinal disease on investigation. Exclusion criteria were abdominal complaints including reflux symptoms, prior abdominal surgery (except appendectomy, hernia repair), or intake of medication other than oral contraception. A Helicobacter-¹³C-breath test was performed to rule out Helicobacter pylori infection.

Secretion stimulating test meal

The test meal was a high caloric, viscous chocolate drink (400 ml, 450 kcal, pH 5.4). The ingredients are listed in **Table S1**. The chocolate powder did not contain any magnetic material, i.e. metal supplements that could function as a MRI contrast marker. The test meal was labelled with 167.5 μ M of MRI contrast agent (CA, DOTAREM[®], Guerbet, Villepinte, France) and 100mg ¹³C-Acetate. In-vitro experiments confirmed acid stability of the test meal. To exclude changes in relaxation time secondary to temperature changes, the test meal was heated to 37° C before intake.

Relationship between meal dilution and T1 relaxation time

Interaction of meal and secretion

To describe the relationship between meal dilution by secretion and the T1 relaxation time (T1), an *in vitro* experiment was performed and analyzed as previously described (12). In brief, T1 depends not only on the CA concentration, but also on the concentration of macromolecules within the test meal. Therefore, a total of 36 test meal samples were measured which were diluted by different amounts of 0.1N HCl and which had different CA concentrations. The effect of the macromolecular content and the effect of the CA concentration in the test meal on T1 was determined and the final relationship computed by nonlinear regression. The resulting exponential relationship is presented in **Figure 1**. The derived CA concentration in the gastric content is directly proportional to the percentage of the meal within the gastric content:

$$[1] \quad \%meal = \frac{100\%}{167.5\mu M} \cdot CA_{\mu M} .$$

In vivo MRI measurements

Subjects were imaged in right decubitus (RD) position in a 1.5 T whole body clinical MRI-System (1.5T Achieva, Philips Medical Systems, Best, The Netherlands) using an abdominal, 4-channel phased-array receive surface coil (SENSE Body-Coil) for image acquisition. A foam rubber mattress and pads at hip and shoulder were used for cushioning and subjects were allowed to move head, arms and legs in between the MRI scans. In a first MRI scan covering the entire upper abdomen (volume scan), fasted gastric content volume was determined. Subsequently, the test meal was ingested in upright sitting position within 2.36 ± 1.22 min. Subjects were repositioned and remained in RD position for the rest of the study period. A volume scan followed by the previously developed fast T1 mapping sequence (secretion scan) was performed every 10 minutes until maximum 120 min. MRI sequence parameters for the volume scan and the optimized secretion scan are given in **Text S2**.

Breath test samples were taken subsequent to all MRI scans and, in addition, up to maximum 240 min after test meal ingestion. These data were used for the validation of the ¹³C-acetate isotope breath test method by MRI and will be presented elsewhere.

DATA ANALYSIS

Volume data

A custom software tool written in MATLAB was used for volume calculation and related image segmentation. Gastric content volume (GCV) defined as content volume without intragastric air was derived by semi-automatic segmentation of the gastric content contours within the images of each volume scan. Based on these contours, a 3D isosurface was generated following the method of Cong and Parvin (15). From the resulting triangular faces and vertices that describe this isosurface, triangular prisms were created and their volume summed up to determine the volume of the segmented gastric content.

T1 maps were reconstructed from the secretion scan data and analyzed using in-house written software in IDL, as described previously (12). Gastric content was semi-automatically segmented in the recorded T1 maps. From the mean T1 values of gastric content, the percentage of intragastric meal volume (%meal) was calculated for each time point applying the determined T1-CA relationship (see Figure 1) and equation 1. Meal volume (MV) and secretion volume (SV) were calculated by first multiplying GCV with the percentage of intragastric MV, i.e. $MV = GCV \cdot \%meal$, and then subtracting the resulting MV from GCV, respectively.

Interaction between gastric secretion and meal emptying

To analyse the interaction between gastric secretion and meal emptying, i.e. to analyze how gastric secretion affects meal emptying and vice versa, the secretion rate and meal emptying rate were calculated by either per-subject non-linear regression to meal and secretion curves or a physiological pharmacokinetic model based on population pharmacometrics (16). The per-subject non-linear regression approach used the following regression equations:

$$[2a] \quad MV(t) = MV(0) \cdot \exp(-k_m \cdot t)$$

$$[2b] \quad SV(t) = SV(0) + (SV_{\max} - SV(0) \cdot (1 - \exp(k_s \cdot t)))$$

with $MV(0)$, $SV(0)$, SV_{\max} , k_m and k_s being the meal and secretion volume at time $t=0$, the maximum achievable secretion volume, the rate constant of meal emptying and the rate constant of the intragastric secretion. For each subject, k_m and k_s values were obtained separately for each MV and SV curve using GraphPad Prism (GraphPad Software Inc., La Jolla, CA, USA). Equations 2a and 2b can equivalently be expressed as two uncoupled linear differential equation, namely:

$$[3a] \quad \frac{dMV(t)}{dt} = -k_m \cdot MV(t)$$

$$[3b] \quad \frac{dSV(t)}{dt} = -k_s \cdot (SV_{\max} - SV(t)) .$$

Here, the term “uncoupled” means that no model parameter occurs in both equations. These differential equations represent a compartment model without interaction, i.e. no coupling, as shown in **Figure 2a**. For this approach, the interaction between secretion volume and meal emptying must be determined by testing for a significant correlation between the rate constants k_m and k_s of each fitted time series.

To incorporate the interaction, i.e. coupling, between meal and secretion into the model, a coupled pharmacokinetic compartment model was applied, see **Figure 2b**. In this model, the amount of meal in the stomach controls the stimulation of secretion, and reciprocally gastric secretion has an influence on meal emptying. This model can be described by the corresponding coupled linear differential equations:

$$[4] \quad \frac{dMV(t)}{dt} = -k \cdot MV(t) - k_{ms} \cdot MV(t) + k_{sm} \cdot SV(t) ;$$

$$[5] \quad \frac{dSV(t)}{dt} = -k_{sm} \cdot SV(t) + k_{ms} \cdot MV(t) .$$

k_{ms} is the part of the meal emptying rate constant which represents the potential of the emptied meal to stimulate secretion. In case of $k_{ms} \ll k$, the emptied meal has a negligible effect on secretion

stimulation. In contrast, if $k_{ms} \gg k$, any meal volume emptied produces the same amount of secretion volume. Thus, the ratio of $k_{ms} / (k + k_{ms})$ quantifies, within a range from 0 to 1, the efficacy of the meal to stimulate gastric secretion (eff_m). k_{sm} describes the factor by which intragastric secretion inhibits the meal emptying process. In case of $k_{sm} = 0 \text{ min}^{-1}$, gastric secretion would not have any effect on meal emptying.

A stable estimate of the three rate constants k , k_{ms} and k_{sm} of the model allows the quantification of how gastric secretion affects meal emptying and vice versa, i.e. the interaction. For this coupled model, numerical parameter estimation is no longer feasible using standard curve fitting. Therefore, the rate constants were estimated using population based nonlinear mixed effects modeling performed with NONMEM® 7.1 (ICON, Dublin, Ireland). Nonlinear mixed effect modeling (nlmem) is commonly applied for the analysis of repeated measurements data, in which multiple individuals have multiple measurements over time, with a nonlinear relationship between the explanatory variable (e.g. time) and the response variable (e.g. volume). The two powerful advantages of the nlmem method are 1) the nlmem method provides the means to analyze repeated-measurements data in which the relationship between the explanatory variable and the response variable can be modeled as a single function, allowing the parameters to differ between-individuals; and 2) the nlmem method allows for the recognition and estimation of two distinct types of variability: between-individual variability and within-individual variability (17). The applied NONMEM code and the used estimation method are given in **Text S3**.

RESULTS

MRI experiments were successfully performed in all 14 subjects. The cushioned RD position was well tolerated by all subjects.

Volume data

Interaction of meal and secretion

The test meal continuously induced gastric secretion in all subjects. The measured and computed volume data of GCV, MV and SV are plotted over time for all subjects in **Figure 3**. At the first measurement time point after the end of meal ingestion $t_1 = 4 \pm 3$ min, SV was already present and showed large inter-individual variation ($SV = 35 \pm 30$ ml). Due to the continuously increasing gastric secretion, GCV decreased much slower over time and showed a different pattern compared to MV. At t_1 as well as during the meal emptying period, gastric secretion in part accumulated at the transition from gastric content to air, forming a “secretion layer” on top of the meal. Meal dilution by gastric secretion over time proceeded mainly from the proximal to distal stomach. These two phenomena are visualized for two exemplary volunteers in **Figure 4a and 4b**.

Interaction of meal and secretion

Based on the volume curves presented in **Figure 3**, the meal emptying and secretion rates were computed using either the per-subject non-linear regression approach or the coupled pharmacokinetic compartment model. The resulting individual fits are presented in the **supplements S4a and S4b**. For the per-subject approach, the rate constant k_s showed a larger inter-individual variability compared to k_m (k_s : $0.035 \pm 0.022 \text{ min}^{-1}$, k_m : $-0.015 \pm 0.005 \text{ min}^{-1}$). k_m and k_s exhibited a significant correlation ($r^2 = 0.75$, $p=0.0001$) suggesting some kind of interaction between gastric secretion and meal emptying, see **Figure 5**.

The coupled pharmacokinetic compartment model allowed the stable estimation and identification of all three rate constants k , k_{ms} and k_{sm} supporting the validity of this approach. However, for some subjects, individual fit quality was inferior to the corresponding per-subject fit quality. This deficit in individual fit quality, however, went together with a more stable estimation of model parameters and the feasibility to quantify the coefficients describing coupling, i.e. to quantify the interaction between meal and gastric secretion. . The population estimates (THETAs) of the rate constants and their respective interindividual variability (ETAs) are listed together with their standard errors (SE) as

well as the residual random error (ERR) of the model in **Table 1**. k and k_{ms} showed low and k_{sm} showed large inter-individual variability. k_{ms} was larger than k_{sm} by a factor of 2.28 ± 0.97 . The efficacy of the meal to stimulate gastric secretion was $eff_m = 0.61 \pm 0.13$. Thus, on average, any meal volume emptied stimulated the production of 61% of its volume as gastric secretion volume.

DISCUSSION

This study assessed and quantified the interaction between meal emptying and meal induced gastric secretion using quantitative MRI and pharmacokinetic modeling.

Test meal composition and caloric load was optimized for maximum secretion stimulation and included fatty acids, carbohydrates, calcium and glutamine from chocolate and enteral nutrition powder. The minimum amount of protein guaranteed negligible denaturation of the meal after exposure to gastric acid as confirmed in previous *in vitro* experiments. The induced stimulation of gastric secretion by the proposed test meal was extensive in all subjects. This became already obvious by simple visual inspection of the acquired imaging data (figure 4) and was confirmed by the numerical separation of MV and SV from GCV (figure 5).

The detected initial secretion volume showed a large inter-individual variation ($SV = 35 \pm 30$ ml). It seems rather unlikely that such a considerable amount of secretion at 4 min after the end of meal ingestion was generated by immediate intense secretion stimulation, but was caused by several factors such as: 1) residual secretion volume prior to meal ingestion that remained during and after drinking, 2) meal dilution by saliva, and/or 3) initial duodenogastric refluates. Due to practical and technical limitations, no data on intragastric volumes were collected during and directly after drinking. Therefore, although we have actually measured the residual gastric content in the fasted stomach prior meal ingestion, no reliable information about these initial emptying, dilution and secretion processes can be gained from the data. Since the focus of this study was the assessment of the interaction of meal emptying and gastric secretion, the analysis started with the first reliable data point where meal emptying had actually started. A comprehensive analysis of initial secretion dynamics after meal ingestion remains the main focus of current research. Another limitation of the applied non-invasive T1 mapping technique is that it cannot differentiate between the meal dilution

by gastric juice, saliva or duodenogastric refluente. Nevertheless, considering the observed amounts of intragastric secretion volumes, meal dilution by gastric juice is much likely the determining factor.

Gastric secretion accumulated in part at the intragastric meal-air interface. This phenomenon was perceived in the MRI images as a “secretion layer” (figure 4). This secretion layer reflected a zone of low CA concentration (i.e. low meal concentration) values. It could not be clearly delineated for all subjects and all time points. A preliminary analysis showed that the majority of the voxels in the secretion layer exhibited CA concentrations around and below 50.25 μM (i.e. 30% meal concentration). A titration experiment, using 0.1 N HCl, indicated that this concentration reflected a $\text{pH} \leq 2$. A detailed quantitative analysis on the association of pH and CA or meal concentration was considered beyond the scope of this manuscript and is focus of ongoing work. In all volunteers the secretion layer was detected in the proximal stomach. A similar proximal location for the secretion layer, which here was determined in the right decubitus body position, can also be expected for the upright sitting position (18). Previous non-invasive findings on meal dilution by secretion of viscous test meals using MRI in supine body position did not report on the formation of a secretion layer (19). In those investigations, meal dilution was reported to proceed from the gastric wall towards the inner viscous meal bolus. In the presented work, based on visual qualitative image analysis, the main dilution of the meal appeared to proceed from the secretion layer along the gravitational vector, i.e. from proximal to distal stomach. A solid analysis, interpretation and discussion of position and/or viscosity dependent intragastric dilution kinetics were considered beyond the focus of this manuscript.

The existence of a so called “acid pocket”, located in the proximal stomach adjacent to the GEJ after meals has been postulated from by pH measurements and γ -scintigraphy, and has been suggested to play an important role in the pathophysiology of acid reflux (1-2). The exact definition of this pocket is still unclear. It has been hypothesized to be a an area of unbuffered gastric juice ‘trapped’ at the

cardia or a film of acid lining the proximal stomach without any significant volume (McColl, Gut April 2010 Vol 59 No 4). From all acquired MRI data, despite the excessive amount of secretion present in the stomach, a pocket of gastric juice could not be confirmed. We hypothesize that the previous findings may be explained by the formation of the detected secretion layer, forming on top of the meal, in the proximal stomach.

As seen in Figure 3, MV and GCV showed different dynamics over time. GCV showed a slow decrease and - in some cases - even remained constant during the early emptying period. MV, on the other hand, decreased continuously after meal consumption and did so at a higher rate than GCV. These findings demonstrate that changes in gastric content volume are not a reliable marker for meal emptying. In the presence of gastric secretion, the change in GCV would profoundly underestimate the true caloric emptying and its delivery to the small bowel. Moreover, it shows the necessity to consider, and ultimately to simultaneously quantify, the stimulated secretion invoked by test meals for each individual, each measurement and potentially every intervention to allow for a robust quantification and comparison of meal emptying. The above finding holds true for all methods that depend on gastric volume measurements such as MRI and 3D Ultrasound (10-11, 20). In comparison, γ -scintigraphy does not depend on the measurement of gastric volumes to determine meal emptying. This technique relies on the detection of the residual intragastric radioactivity that was bound to the test meal to measure meal emptying. For γ -scintigraphy, however, it is crucial to prevent the dissociation of the radiotracer from the solid phase into the liquid phase, which would empty faster (21). Currently, only two radioactive ^{99m}Tc labeled test meals, i.e. egg white and liver, have been validated for their stability of radiolabel binding (21). To date, the proposed quantitative MRI method does not yet provide the means to separate gastric secretion from an inhomogeneous solid test meal. However, the MRI method potentially allows any composition of (non-magnetic) nutrients within a viscous liquid test meal to be evaluated with regard to meal emptying, gastric secretion as well as gastric motor function without radiation exposure.

Gastric secretion should not only be considered as a correction factor for gastric content volume measurements, but also as a potential interacting factor in the meal emptying process (5). Recently, a novel linear exponential function (LinExp) was introduced for the analysis of gastric content emptying and compared to the standard power exponential approach (PowExp) (22). The LinExp model is useful for gastric content volume data, because it can fit an initial volume plateau or an increase caused by gastric secretion via a parameter κ . The LinExp (as well as PowExp) model is a valid fitting approach if only gastric content volume data is assessed, however, inappropriate for the quantification of gastric secretion rate and its interaction on meal emptying. For such analyses, meal volume and secretion volume must be assessed separately, and modeled as the sum of two functions, as demonstrated in this work.

In this study, the interaction between meal emptying and gastric secretion were analyzed using two different mathematical approaches. The first approach used the traditional per-subject fitting routine and allowed only the detection of a potential correlation between secretion rate and meal emptying rate. The second approach applied a population based pharmacokinetic compartment model that allowed quantifying the extent of this interaction and its direction. The application of population pharmacometrics to the presented data prevented typical problems well known for the traditional fitting of nonlinear parameterized curves which only works for rather simple cases. If multiple parameters are to be fitted, the fitted coefficients can be highly ambiguous, because parameters compete with each other in predicting the curve: this is called parameter correlation. The same is true for individual differential equations fitted to time series, as in the first presented mathematical approach. In the population approach, multiple curves from one study are fitted with the statistical constraint that all curves have some features in common, i.e. that the estimated parameters are from a Gaussian distribution. With this assumption, stable fits can be obtained even for individual curves that failed to give consistent results with the standard approach.

The inferior individual fit quality of the compartment model approach observed for some subjects (Figures S4a and S4b), demonstrated that a good fit is not a quality in itself. The strength of the population approach is that the estimated coefficients are much more stable because of the mutual "borrowing strength" between fits, which in turn makes it possible to obtain stable estimates of coefficients describing coupling. The per-subject fitting approach showed a significant correlation of $r^2 = 0.75$ between the meal emptying rate and the secretion rate. However, it did not provide information on the direction and the extent of interaction. From figure 1 it is not clear whether a higher secretion rate led to a faster meal emptying or a faster emptying rate led to increased secretion. The proposed population pharmacokinetic compartment model quantified the rate constants k_{ms} and k_{sm} that describe the influence of meal and secretion volume on meal emptying rate and secretion rate, respectively. The effect of meal emptying on the secretion rate, i.e. k_{ms} , was larger than the effect of secretion on meal emptying, i.e. k_{sm} (by a factor of $k_{ms}/k_{sm} = 2.28 \pm 0.97$). The estimation of k_{ms} was robust and showed low inter-individual variability (low standard errors for THETA and ETA), whereas the estimation of k_{sm} showed large standard errors (Table 1). The majority of the emptied meal volume had a stimulating effect on gastric secretion. The population pharmacokinetic model quantified the efficacy of the meal to produce gastric secretion to be $eff_m = k_{ms}/(k+k_{ms}) = 0.61 \pm 0.13$, i.e. any meal volume that was emptied stimulated the production of 61% of its volume as gastric secretion. These results demonstrate the feasibility of applying standard pharmacokinetic compartment models to quantify the interacting effect of meal and secretion from quantitative MRI data.

In conclusion, as demonstrated in this work and in contrast to all other present methods that are applied for the measurement of gastric emptying, the validated quantitative MRI method – together with population pharmacokinetic modeling - allows the simultaneous assessment of meal emptying and gastric secretion and the quantification of the interaction between meal and secretion. The combined MRI and pharmacokinetic approach represents a promising framework for studies aiming

for a detailed understanding of the (patho)physiology of gastroesophageal reflux, gastric emptying and gastric motor function.

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MS & AS designed the research study, performed the research, analyzed the data and wrote the manuscript. JC performed the research and analyzed the data. DM analyzed the data. OG & WS & MF designed the research study.

Competing interests: the authors have no competing interests.

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Tables

Table 1. The computed parameters of the population pharmacokinetic model

Rate constant	Population estimate <i>THETA</i> [min ⁻¹]	SE [%] of <i>THETA</i>	SE [%] of <i>ETA</i>	SE [%] of <i>ERR</i> (1)
<i>k</i>	0.007	2.0	21	15
<i>k_{ms}</i>	0.011	2.4	25	
<i>k_{sm}</i>	0.005	64	109	
<i>THETA</i> – population estimate of rate constant <i>ETA</i> – interindividual variability of rate constant <i>ERR</i> – additive residual random error of the model				

Figure legends

Figure 1. The relationship of the relaxation time T1 (s) and the contrast agent concentration (μM) of the meal. The T1-CA relationship follows an exponential curve with $\beta = 0.13 \mu\text{M}^{-1}$ and $T_{10} = 2.58 \text{ s}$. The vertical dashed lines indicate the corresponding percentage of meal as determined using equation 1.

Figure 2. The two different compartment models applied to determine the interaction of meal and secretion. The meal (MV) and secretion (SV) compartment are displayed as grey circles. Corresponding meal emptying, secretion and interacting rate constants are indicated as thin arrows. The ingestion of the test meal is considered a bolus application to the meal compartment (bold arrow). A) Schematic of compartment model 1 with k_m and k_s being the rate constant of meal emptying and intragastric secretion, respectively. No interaction is considered between meal and secretion compartment. B) Schematic of model 2 with k_{ms} , k_{sm} describing the influence of meal and secretion volume on the secretion and meal emptying rate, respectively. k describes the rate constant of the meal volume that is emptied without stimulating gastric secretion.

Figure 3. The volume curves for GCV, MV and SV. MV exhibited a linear to exponential emptying pattern. Due to the continuous increase in SV, $\text{GCV} = \text{MV} + \text{SV}$ decreased at a lower rate and with different patterns than MV.

Figure 4. Axial MRI images acquired during the volume scan of two different subjects at different time points along the study period. In the MRI images at the first imaging time point the stomach contour is outlined and the meal volume is indicated by the horizontal white arrow. In these MRI images, gastric secretion can be identified as brighter MR signal compared to meal and intragastric air (black). In the second MRI image kidneys (K) and the liver (L) are marked for better anatomical

orientation. A) MRI images of a subject which exhibited an intragastric secretion layer throughout the complete study period. The secretion layer (bright signal) formed and continuously increased at the meal-air interface as clearly recognizable at time points 3, 41 and 81 min. B) MRI images of a subject which showed good intragastric mixing in this study. The bright MR signal from gastric secretion is also discernable; however no clear secretion layer is detectable. Rather, an increasing meal dilution gradient by secretion from proximal to distal is observed over time.

Figure 5. Correlation plot of k_m and k_s . A significant correlation was detected between the meal emptying rate (k_m) and secretion rate (k_s) as computed by the per-subject fitting approach.

Supplemental material

Table S1. Test meal ingredients and characteristics

Text S2. MRI sequence parameters used for the volume scan and secretion scan.

Text S3. The NONMEM code for the population estimation of model parameters. The model parameters K, K12 and K21 are synonyms for the rate constants k , k_{ms} and k_{sm} , respectively.

Figure S4. Individual fits for MV and SV for model 1 and 2. A) The individual fits (red) for MV and SV (black dots) as computed by the traditional separate fitting approach. B) The individual fits (red) and the population fits (grey) for MV and SV (black dots) as computed by the population pharmacokinetic model approach.